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Invited Article

Wangiella Dermatitidis Infections: A Paradigm of the Opportunistic Mycoses Caused by Black Yeasts and Moulds

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INTRODUCTION

In the tropical and subtropical regions of the world, a significant spectrum of phaeoid or dark-pigmented fungi capable of causing mycoses exists. Pigmented fungi are characterized by having melanin in the cell walls of their saprophytic and parasitic forms. They have a broad spectrum of clinical features, ranging in severity from superficial and mild cases of pityriasis nigra, to deep-seated and fatal cases of phaeohyphomycosis of the central nervous system[1,2].

Human infections caused by phaeoid fungi of the cutaneous and subcutaneous tissues can be separated into three categories: chromoblastomycosis, black grain mycetomas, and phaeohyphomycosis[3]. It is important to note that the terms "chromoblastomycosis" and "mycetoma" have been clinically recognized. The umbrella term "phaeohyphomycosis" was coined in 1974 by Libero Ajello to cover the mycotic diseases caused by phaeoid fungi that do not fit into the classic concepts of chromoblastomycosis and black grain mycetomas[4]. The fundamental difference among these disease entities lies in the tissue forms assumed by their respective etiologic agents. The fungi that cause chromoblastomycosis and black grain mycetomas have phaeoid muriform cells and granules respectively as their *in vivo* diagnostic hallmarks. Phaeohyphomycosis is characterized by the development of phaeoid, septate, and filamentous hyphae in tissue[5]. Later, Ajello expanded the definition of phaeohyphomycosis to include all superficial, cutaneous, subcutaneous, and systemic infections of humans and lower animals caused by phaeoid fungi. These infections have multiple microbial etiologies[6,7].

It is pertinent at this point to provide an explanation of the terms "phaeoid" and "muriform cells". The term "dematiaceous", which traditionally has been used to describe dark-pigmented fungi, was found to be epistermlogically incorrect by Pappagianis and Ajello in 1994[8]. Later, it was recommended that the term "dematiaceous" be replaced by the new term "phaeoid" derived from a Greek word that means "dark" or "dusky"[9]. The rationale for this change stemmed from thd fact that the Greek root for "dematiaceous" refers to a "bundle" or "bunch" and has no reference to color.

In chromoblastomycosis, all etiologic species produce the same type of round to polygonal, thick-walled, dark-brown cells divided into more than one plane by cross walls. These tissue form cells were formerly referred to as "sclerotic cells". My co-workers and I pointed out, in 1984, that Medlar's term "sclerotic cells" does not fit the definition of a sclerotium in contemporary mycologic thought[10]. In Hawksworth et als' "Dic-

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tionary of the Fungi", a "sclerotium" is defined as "a mass of hyphae". We proposed replacement of the term "sclerotic cells" by "muriform cells" as used for the characteristic cells in tissue in chromoblastomycosis. The latest edition of "Dictionary of Fungi" accepted "muriform cells" as we had proposed[11].

MICROBIOLOGY OF *WANGIELLA DERMATITIDIS*

Wangiella dermatitidis is a phaeoid hyphomycete with a yeast form that is an important etiologic agent of phaeohyphomycosis. Dr. kaiichiro kano in 1933 originally isolated this fungus in Japan from a human skin lesion and described it in 1934 as a new agent of chromoblastomycosis under the name *Hormiscium dermatitidis*[12]. Subsequent to Kano's report, other investigators reassigned his organism and similar phaeoid yeast-like etiologic agents of chromoblastomycosis and phaeohyphomycosis to several taxonomically diverse genera.

In 1977, McGinnis erected a new genus *Wangiella*[13,14]. It was characterized by its initial yeast-like growth on synthetic media followed by the production of mycelium that bore conidia discharged from phialides without collarettes. Later in 1977, de Hoog considered it to represent a species of the genus *Exophiala* because of the annellidic mode of conidiogenesis and hence offered the new combination *Exophiala dermatitidis*[15].

Recently McKemy from the State University of New York in Syracuse investigated the phylogenetic relationships of *Phialophora* and other related genera based on ribosomal DNA sequence data[16]. His findings cogently show that the genus *Wangiella* should be separated from the genus *Exophiala*. McKemy and his colleagues emended the genus *Wangiella* to accommodate phialides with distinct collarettes, acropetally produced chains of conidia, in addition to those already described, such as, phialides without collarettes and yeast-like cells. They also reassigned the species *Phialophora heteromorpha* to the genus *Wangiella*, as *W. heteromorpha*[17].

In 1984 we critically studied 26 isolates that had been identified as *W. dermatitidis*, including Kano's original isolate[10]. Twenty-one of these isolates proved to be *Wangiella dermatitidis* on the basis of their colonial and microscopic morphology, thermotolerance, decomposition of tyrosine, and exoantigen tests. The remaining five isolates were identified as either *Exophiala jeanselmei, E. moniliae*, or *Fonsecaea pedrosoi*.

The isolates of *W. dermatitidis* varied widely in their gross cultural aspects. They formed either smooth, pasty yeast-like phaeoid colonies, or black yeast-like colonies with scattered tufts of aerial mycelium. The single consistent microscopic morphology of *W. dermatitidis* is the formation of phialidic conidiogenous cells without distinct collarettes. Its conidia are unicellular, globose to subglobose, smooth, hyaline. They aggregate in clusters at the apex of phialides and/or along the conidiophores. Occasionally, phialides with distinct collarettes and phialoconidia are also produced by *W. dermatitidis*.

In a subsequent study, we described a new anamorphic fungus, *Sarcinomyces phaeomuriformis*, to accommodate those phaeoid isolates that had been incorrectly referred to as the granular colony form of *W. dermatitidis*[18]. This species produces stable, dry, black, granular, slow-growing, and mulberry-like colonies. *Sarcinomyces phaeomuriformis* differs from other members of its genus by forming multiple broad-based buds and chains of budding cells.

There is a close relationship between *W. dermatitidis* and *S. phaeomuriformis*. A recent molecular biological study has validated that these organisms should be considered to be two distinct species[19].

In the late 1980s, Dr. Inn-Ki Chun from Chonnam University saw a Korean patient with subcutaneous phaeohyphomycosis caused by *W. dermatitidis*. In that isolate, we encountered unusual multicellular structures in addition to the

characteristic diagnostic features of *W. dermatitidis*. Several endoconidia were contained within an intact enlarged cell. Rupture of its cell wall permited the release of the endoconidia, and a hyphal germ tube emerged from the endoconidia. This unusual endosporulating structure resembled similar structures formed by members of the genus *Phaeotheca*. This morphology, accordingly, was described by us as a new synanamorph of *W. dermatitidis*[20].

I have to mention a series of studies on the pathogenicity and virulence of wild-type and melanin-deficient *W. dermatitidis* strains carried out by Dixon and his colleagues. A dramatic decrease in the virulence of melanin-deficient *W. dermatitidis* mutants was observed. The melanin synthesis by pigmented fungi is thought to be involved in the pathogenesis of a number of phytopathogenic fungi and it may also function in the pathogenesis of infections in humans and other animals[21,22].

CLINICAL SPECTRUM OF *WANGIELLA DERMATITIDIS* INFECTIONS

The nomenclature of infections caused by *W. dermatitidis* has been in a state of confusion. Among phaeoid fungi, this fungus has an especially broad spectrum of clinical features, ranging in severity from superficial and mild, to deep-seated and fatal. Another cause of controversy is the polymorphism of its fungal elements in tissue.

In a study published in 1993, we critically reviewed the described cases of *W. dermatitidis* infections with their literature descriptions, clinical photographs, and histopathological tissue sections, focusing especially on clinical features, the patients' underlying conditions, sites of infection, the hoste' histopathologic reactions, and the fungal morphologies in tissue. As a result we confirmed 37 well documented cases of *W. dermatitidis* infections[23]. The human infections caused by this mould can be separated into three groups: (1) superficial infections, such as keratomycosis and onychomycosis; (2) cutaneous and subcutaneous phaeohyphomycosis; and (3) visceral or systemic phaeohyphomycosis. The patients ranged in age from 10 to 79 years with a mean age of 39 years. Nineteen of the 37 patients were from Japan, 11 from the United States, two from Taiwan, and one each from Brazil, former Czechoslovakia, The Netherlands, South Korea, and Spain. Several additional cases have been reported from France, Japan, Korea, United Kingdom, and the United States. It is noteworthy that most of the recent cases were documented in the United States and Europe. *Wangiella dermatitidis* is an important agent of opportunistic systemic phaeohyphomycosis with a marked tendency to invade the central nervous system. Nineteen patients had associated diseases or predisposing conditions, including angina pectoris, chronic granulomatous disease, diabetes mellitus, and intravenous heroin addiction.

Superficial infections caused by *W. dermatitidis* comprised cases of keratomycosis and onychomycosis, each of which should be properly designated as corneal phaeohyphomycosis and ungual phaeohyphomycosis. In a recent French case of *W. dermatitidis* keratitis following keratoplasty reported by Dr. Evelyn Gueho[24] from the Institute Pasteur in Paris, the slit-lamp aspect of keratomycosis showed numerous fungal infiltrates, adjacent to the corneal sutures. Diagnosis was established by positive direct examination of cultures of *W. dermatitidis* from corneal buttons, iris biopsies, and ablated sutures.

In a Japanese case of onychomycosis caused by *W. dermatitidis*, which was successfully treated with a topical solution of bifonazole, direct potassium hydroxide examination of the nail tissue demonstrated clusters of phaeoid spherical cells, toruloid hyphae, and septate hyphae[25]. The colonies and microscopic morphology of the isolated *W. dermatitidis* predominantly consisted of yeast-like cells. This was the first documented case of fungal melanonychia caused

by this organism. Following our report, two similar cases due to *W. dermatitidis* have been documented[26,27]. Currently, the list of etiologic agents of confirmed cases of phaeoid fungi causing fungal melanonychia includes *Alternaria alternata, A. humicola, A. pluriseptata, Lasiodiplodia theobromae, Chaetomium perpulchrum, Cladophialophora carrionii, Curvularia lunata, Nattrassia mangiferae*, and *Pyrenochaeta unguis-hominis*.

Other infections caused by *W. dermatitidis* represented cases of cutaneous and subcutaneous phaeohyphomycosis. In 17 patients, the infections were limited to the skin and soft tissues. The face and neck were the most affected sites. In a Japanese female patient with cutaneous phaeohyphomycosis, she demonstrated facial nerve palsy, and neurological and radiographic manifestations of probable involvement of the central nervous system.

Histopathologically, branched phaeoid mycelium is one of the parasitic tissue forms of *W. dermatitidis* in cutaneous and subcutaneous lesions. Its parasitic morphology in lymph nodes shows phaeoid spherical cells, toruloid hyphae, and mycelium contained within foreign body giant cells. In a 1985 report from the United States, an intravenous drug addict with endocarditis caused by *W. dermatitidis* showed abundant branched mycelium in his tissues[28].

A recent Japanese case of fatal systemic phaeohyphomycosis caused by *W. dermatitidis* developed the initial lesions in the cervical lymph nodes without any skin lesions[29]. The lymph node tissue had undergone granulomatous changes and dark-pigmented hyphae were seen within giant cells. Later, the patient developed pancreatic and duodenal lesions, and finally intracranial lesions in the right frontal and parietal lobes that were demonstrated clearly by CT scanning and MR imaging. *W. dermatitidis* is well known as a dermotropic and neurotropic fungus. Its fatality rate is 32%, which is significantly higher than the other etiologic agents of phaeohyphomycosis, such as *E. jeanselmei*.

W. dermatitidis shows a wide range of fungal morphologies in tissues. They may be in the nature of dark-walled, short, septate, branched or unbranched hyphal elements, catenulate spherical cells, as well as isolated spherical cells. In skin and subcutaneous tissues, this mould tends to develop in the form of spherical cells. The spherical cells occasionally resemble the muriform cells of chromoblastomycosis, but differ by having thinner walls and divide either by budding or septation in a single plane. In other organs, the mycelial form of the fungus is generally encountered.

Where tissue reactions and fungal morphologies *in vivo* were concerned, the granulomatous lesions caused by *W. dermatitidis* predominantly contained spherical cells of the pathogen. On other occasions, however, mycelium was the dominant tissue form. From a clinical and histopathologic point of view, all of the infections caused by *W. dermatitidis* correctly should be referred to as cases of phaeohyphomycosis[10,23].

The management of infections caused by *W. dermatitidis* is difficult and often frustrating. Small and localized cutaneous and subcutaneous lesions, however, are amenable to surgical excision. When the infection is widespread, deep-seated, or visceral and disseminated, chemotherapy with either amphotericin B or flucytosine or combination therapy with both of these antifungal agents should be attempted. New antifungal agents, such as itraconazole and terbinafine, show therapeutic promise. Clinical and experimental experience will be needed before the most effective dosage and treatment schedules can be determined[30,31].

CONCLUSION

At one time, *W. dermatitidis* was considered to be a pathogen occurring primarily in Japan and adjacent Asian countries. Now it has been found to be an important emerging phaeoid fungal pathogen having a world-wide distribution. Today the problems caused by black mould and

yeast infections represent some of the most recalcitrant of all fungal diseases and a challenging public health problem.

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